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# Management of hyperglycemia in patients with diabetes me chronic renal failure

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## Abstract

Diabetes mellitus is recognized as a leading cause of chronic kidney disease an failure. Chronic renal failure is associated with insulin resistance and, in advanc decreased insulin degradation. Both of these abnormalities are partially reverse of dialysis. Except for diet with protein restriction, patients with diabetes shoul with insulin. The management of the patients with hyperglycemia and chronic r close collaboration between the diabetologist and the nephrologists. This collab important so that the patient will not be confused and will not lose confidence t Furthermore good glycemic control in these patients seems to reduce microvas macrovascular complications.

Keywords: hyperglycemia therapy, diabetes, chronic kidney disease

Diabetes mellitus is a major health problem of increasing magnitude worldwide on cardiovascular morbidity and mortality[1]. Moreover diabetes mellitus is recog cause of chronic kidney disease and end-stage renal disease in the United States Countries[2]. Large epidemiological studies have shown that one third of the pati or renal transplant recipients are diabetics, predominantly with type 2 diabetes[3] designed randomized studies have provided convincing evidence on the value o preventing both micro and macrovascular disease[4]. The UK Prospective Diabet that intensive treatment of patients with newly diagnosed diabetes reduced the r infarction by 16%, amputation or death from peripheral vascular disease by 35% infarction by 6%, nonfatal myocardial infarction by 21%, fatal sudden death by by 39%. Every 1% reduction in glycosylated hemoglobin was associated with r 21% for any end point related to diabetes 21% for diabetes related deaths, 14% infarction and 37% for microvascular complications. Therefore the glycemic co important for the prevention of diabetic complications[5, 6].

## The problem of diabetic nephropathy

In the past is has been believed that fewer patient with type 2 diabetes develope

that proteinuria in these patients had relatively better prognosis compared to pa diabetes. Well designed prospective studies have shown that once proteinuria d end-stage renal disease is similar in both types of diabetes[7]. Moreover recent ep have shown that end-stage renal failure has increased dramatically in patients w The reason for this is that the treatment of hypertension and coronary heart dise life expectancy of the patients with type 2 diabetes and larger proportion of thei nephropathy and end-stage renal disease[8,9].

## The role of kidney in the metabolism of insulin in and in renal failure

In non-diabetic individual, 40-50% of insulin secreted by pancreas is extracted passage through the liver[10,11]. Consequently, the kidney plays a smaller role in secreted in non-diabetic individual than in disposing of insulin injected into dia 1). Endogenously secreted insulin is degraded by liver, exogenous insulin is pri the kidney.

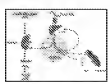

Figure 1.

Metabolism of insulin. Insulin is freered at the glomerulus and then e reabsorbed by the proximal tubule. Of the total renal insulin clearanc 60% occurs by glomerular filtration and 40% by extraction from perit

(more ...)

The kidneys play an important role in the clearance of insulin from the systemic has a molecular weight of 5734 and is therefore freely filtered at the glomerulus reabsorbed by the proximal tubule. Of the total renal insulin clearance, approxir glomerular filtration and 40% by extraction from peritubular vessels. Insulin in enters the proximal tubular cell by carrier-mediated endocytosis and is then tran lysosomes where it is metabolized into amino acids that are released into peritul diffusion. In addition to luminal clearance via glomerulal filtration, the kidneys post-glomerular peritubular circulation (Figure 2). These intrarenal pathways of involve both receptor and non-receptor mediated uptake. The net effect is that l insulin appears in final urine[12–14].

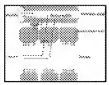

Figure 2.
Intrarenal pathways of insulin removal. Filtrered insulin is internalized endocytosis and thereafter degraded into amino acids into the peritut Insulin removed from postglomerular peritubular vessels binds to the cell membrave. (more ...)

In patients with advanced renal failure basal plasma levels of insulin, proinsulin elevated. The renal clearance of C-peptide is greater than of insulin in renal insu the use of C-peptide concentration as an index of insulin secretion in these patie During the early phase of renal insufficiency, impaired renal insulin clearance is blood flow, but as renal function declines, the effect of reduced blood flow is ag of tissue extraction of insulin[13]. As renal failure progresses, peritubular insulin u compensates for the decline in degradation of filtered insulin until the glomerul decreases to less than about 20 ml/min, after which insulin clearance decreases, increases, and overall requirements for insulin decline[12,16–18]. There is evidence that renal failure suppresses insulin metabolism in extrarenal sites, e.g. in skelet liver. Insulin-dependent diabetic patients often occur a decrease in insulin requi patients with residual β cell function, the need for exogenous insulin may disap with endstage renal disease and hemodialysis occur hypoglycemia because of p of circulating insulin, altered dietary and exercise patterns[20].

Under normal circumstances, the capacity of renal tubules to absorb filtered ins saturation does not occur, therefore insulin clearance normally is constant over concentration.



## The role of insulin resistance

Patients with renal failure have impaired insulin sensitivity with consequent abr metabolism. The underlying mechanism is not clear, but an increase of glucone

reduction of hepatic and/or skeletal muscle glucose uptake and an impairment c glucose metabolism due either to decreased oxidation to carbon dioxide and wa synthesis of glycogen may be involved[18,21,22]. The exact mechanism of insulin r with renal failure is still debated. There are some controversies in the literature, clinical studies indicate that in uremia glucose production and uptake in the live skeletal muscle is the primary site of insulin resistance[18,23]. Moreover glucogen abnormality seems to be of great importance, as the rate of glucose oxidation is

Other factors contributing to insulin resistance in uremic patients are an accum toxins and an excess of parathyroid hormone. The role of uremic toxins was sup observation that hemodialysis improved insulin sensitivity[24–26]. Some studies ha intravenous therapy with calcitriol (1,25-dihydroxyvitamin D) and hyperparath enhanced insulin sensitivity and improved glucose tolerance. Decreased tissue c because of anemia also contributes to insulin resistance in uremia as evidenced increase in insulin sensitivity after correction of anemia by erythropoietin[27,28].

## Insulin secretion in renal failure

As glomerular filtration decreases below 50 ml/min insulin secretion seems to b probably due to the presence of metabolic acidosis, the parathyroid hormone ex the elevation of intracellular calcium concentration and decrease of the cellular Na-K-ATPase pump activity in the pancreatic β cells. Experimental studies hav changes may be prevented by prior parathyroidectomy or by the administration channel blocker verapamil and that the effect of metabolic acidosis to insulin se reversed by hemodialysis[13,29–31].

There are some controversies about the effect of erythropoietin therapy on insul studies showed increase of insulin secretion and decrease of blood glucose leve and other studies showed no change in insulin secretion after an oral glucose lo

## Insulin requirements in diabetes mellitus with re

Insulin requirements show a biphasic course in patients with diabetes and renal beginning glucose control deteriorates because of insulin resistance, therefore n to achieve glycemic control. In advanced renal failure with creatinine clearance need for insulin is lower or even the cessation of insulin may be necessary. The decreased because of less caloric intake in uremic patients. With the institution need for insulin changes because the insulin sensitivity and liver metabolism im

In both non-diabetic and diabetic subjects with chronic renal failure spontaneou develop because of decreased caloric intake, reduced renal gluconeogenesis, im counterregulatory hormone epinephrine due to the autonomic neuropathy, conc and decreased metabolism of drugs that might promote a reduction in plasma gl such as alcohol, nonselective blockers, and disopyramide[23,36,37]. The plasma elir significantly increased in patients with renal insufficiency when clereance of cr 40ml/min, therefore in these patients the dose adjustment of disopyramide is ne

## Glycemic control in patients with diabetes mellitu failure

Measurement of the glycated hemoglobin (HbA1c) seems to be the most accura glycemic control in patients with diabetes. However there are some limitations insufficiency, due to interference from carbamylated hemoglobin that leads to f HbA1c level. Other factors that affect the accuracy of the HbA1c measurement cell life span, recent transfusion, iron deficiency, accelerated erythropoesis due therapy, and metabolic acidosis[38–43]. Despite this limitations results on the rang percent appear to estimate glycemic control similarly to patients without advan while values over 7.5% may overestimate the extent of hyperglycemia.

Self blood glucose monitoring (SMBG) permits estimation of chronic glycemic American Diabetes Association (ADA) recommends that patients with type 1 d glucose at last three times daily, and type 2 diabetes patients that are treated wit hypoglycemic drugs monitor blood glucose daily[44,45]. Self-blood glucose monit important in type 1 diabetes, because their blood glucose concentrations are les day than are those in patients with type 2 diabetes.

Fasting blood glucose levels < 140 mg/dl, < 200 mg/ dl one hour after meal anc between 6- 7% in type 1 diabetes and between 7-8% in patients with type 2 dial hemodialysis are considered acceptable[46].

Excellent glycemic control has not been emphasized as much in diabetic dialys those without renal failure because of the possible precipitation of hypoglycemi control, especially with fluctuating dietary intake[47].

## Management of patients with diabetes mellitus a kidney disease

The management of diabetic patients with advanced kidney disease include diet

restriction and oral agents or insulin. Patients with renal failure are often confus recommendations and have the impression that different specialists have contra give opposing nutritional advice.

In patients with type 1 diabetes insulin therapy imposes regularity in food intak intake of carbohydrates. A dietary pattern in these patients should include carbc vegetables, whole grains, legumes, and low-fat milk. Moreover, monitoring car carbohydrate counting, exchanges or experienced-based estimation remains a k achieving glycemic control and maintain a stable body weight.

Most of the patients with type 2 diabetes are obese, with insulin resistance and secretion. These patients must be encouraged to loss weight with hypocaloric d Protein restriction is in practice replaced by carbohydrates or fat in order to mai caloric intake. It has been shown that both short-term and long-term increases i ratio are accompanied by an improvement in the action of insulin [49]. However b 55% of carbohydrates hypertriglyceridemia may develop. On the other hand inc saturated fat ratio was accompanied by the inhibition of insulin action, while th monounsaturated or polyunsaturated fats did not rise the insulin resistance[50]. Th appropriate to compensate this reduction in protein caloric intake by carbohydr of both types of diabetes with renal failure should be advised to go on a protein compensate the loss in calories by carbohydrates. The dietary management in th close collaboration between the dietician, the diabetologist and the nephrologist

## Pharmacological treatment of hyperglycemia in p diabetes mellitus and advanced kidney dis

The antihyperglycemic drugs available for the treatment of type 2 diabetes incl (sulphonylureas and meglitinides), metformin, -glucosudase inhibitors, the thia 1) and insulin, while patients with type 1 diabetes mellitus are treated with insu

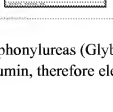

Table 1
Oral anti hyperglycemic agents (adapted from RW Snyder and JS Be Dialysis 2004, Vol 17, No 5, pp 365-370)

Sulphonylureas (Glyburide, Glipizide, Glimepiride) are strongly protein bound, albumin, therefore elevated drug plasma levels cannot be efficiently reversed b

administration of these drugs in patients with end-stage renal disease requires c dosing and the routes of elimination.[51] .

Glyburide has weak metabolites that are excreted in the urine and accumulate i failure. This drug can be given at reduced dose if the GFR is above 50 ml/min, in more sever renal impairment.

Glipizide is metabolized in the liver into several inactive metabolites. Less than Glipizide is excreted unchanged in urine and about 60% is excreted as metaboli metabolites accumulate in patients with renal failure and, one of them may hav activity, that does not cause hypoglycemia. Moreover, Glipizide clearance and short (two to four hours), therefore dose adjustment in patients with reduced GI Glipizide should probably be the sulphonylurea of choice in patients with renal is not available in Greek market at present time.

Glimepiride is metabolized in the liver, the elimination half-time is about 5-8 h of a dose appears in the urine. Virtually all of the urinary excretion is as metabo in patients with renal failure. Glimepiride may cause prolonged hypoglycemia i dysfunction, so the drug should be used cautiously, and the dose of this drug m patients with a reduced GFR.

Repaglinide is a drug that is exclusively metabolized in the liver, with a half-eli hours and is excreted in the bile and stool. Only 10% of the total dose appears i concentration and elimination half-life are increased in patients with renal failu Nevertheless, dose reduction is not necessary in these patients[54].

Nateglinide, is a drug with hepatic metabolism and elimination half-life of abou Several of the metabolites are active and accumulate and in patients with impai causing hypoglycemia. Therefore this drug should be used cautiously in such p

Metformin is primary excreted unchanged in the urine. Patients with renal failu susceptible to drug accumulation and lactic acidosis. Therefore this drug is cont creatinine creatinine clearance is below 60 ml/min[51].

The thiazolidinediones (Pioglitazone, Rosiglitazone) are virtually completely m liver, each forming several metabolites. For both drugs there is no accumulatio the major metabolites in the setting of renal insufficiency. These drugs may cau congestive heart failure. Plasma volume increases in patients treated with thiaz consequent anemia due to hemodilution. The risk for edema is more prominent used in patients in combination with insulin[51,57,58]. Given the risk of edema for failure these drugs should be avoided in patients with advanced kidney disease, have preexisting heart failure. Whether these drugs should be avoided in patien uncertain.

Alpha-glucosidase inhibitors such as acarbose or miglitol are renally excreted v accumulation in renal dysfunction and are contraindicated in patients with renal

## Use of insulin in chronic renal failure

Chronic renal failure is associated with decreased renal and hepatic metabolism decreased clearance and metabolism of insulin, the metabolic effects of insulin longer and the risk for hypoglycemia increases. According to current recommer adjustment is required if the GFR is above 50 ml/min. The insulin dose should approximately 75% when the GFR is between 10-50 ml/min and by as much as is less than 10 ml/min[51,52,59].

It is of great importance that the net effect on glycemic control will vary from p therefore dose adjustment may be necessary.

The 2005 K/DOQI guidelines suggest that in patients with end-stage renal disea should be encouraged for glycemic control, and oral antihyperglycemic drugs s exception of Glipizide[60].

Insulin regimens are the same as in patients without renal insufficiency[51,61,62].

The pharmacokinetics of various insulin preparations have not been well studie varying degrees of renal dysfunction, and there are no absolute guidelines defin dosing adjustment of insulin that should be made based on the level of GFR [51]. stage renal disease some suggest that long-acting insulin preparations should be support that such agents should be used.

Patients treated with continuous ambulatory peritoneal dialysis or continuous cy dialysis (CAPD and CCPD) can be treated with intraperitoneal insulin. This reg continuous insulin infusion, eliminates the need for injections and provide a mc of absorption[63–65]. The disadvantage of this therapy is that there is an additional contamination of dialysate during injection of the insulin into the bags, the neec of insulin because of losses of spent dialysate and increased risk of peritoneal proliferation[66] and hepatic subcapsular steatosis[63]. Moreover the absorption of i significantly vary among patients or may decline over time due to acquired abn peritoneal membrane.

In conclusion patients with diabetes mellitus and advanced kidney disease shou with protein restriction and, preferably by insulin regimen. Oral hypoglycemic avoided because of risk of hypoglycemia, with exception of glipizide or repagli should be adjusted on the basis of glucose values obtained by home glucose me glucose monitoring). In addition to self-monitoring of blood glucose, while peri glycated hemoglobin (HbA1c) permits estimation of chronic glycemic control.

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